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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LACOURCIERE, KAREN A	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/622,719	LOEWENHEIM, HUBERT	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28,29,31,32,34,36-47,55,57,58 and 62-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28,29,31,32,34,36-47,55,57,58 and 62-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *May 12, 2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

Reference WO 97/04762, cited on PTO form 1449, filed May 12, 2003, has only be considered for the information provided in the English abstract, as the full translation was not provided.

Reference Shankland et al., cited on PTO form 1449, filed May 12, 2003, has only be considered for the information provided in the abstract, as the full reference was not provided.

Claim Rejections - 35 USC § 112

The rejections of record of claims 41, 44, 45 and 48 under 35 USC 112, second paragraph are withdrawn in response to Applicant's amendments filed May 12, 2003, however new rejections under 35 USC 112, second paragraph are set forth below.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 44 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 44 is indefinite due to the recitation "derived from". It is unclear what type of changes and the degree of change that can occur in a retrovirus, adenovirus or adeno-associated virus for a vector to be considered "derived from" such virus, rather

than being considered a completely unrelated vector. The scope of the vector used in the claimed methods is unclear and, therefore, the scope of the claimed methods cannot be determined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28, 29, 31, 32, 34, 36-47, 55, 57, 58 and 62 are maintained as rejected and claims 63-66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 28, 29, 31, 32, 34, 36-47, 55, 57, 58 and 62-66 are drawn broadly to methods of treating perception deafness or promoting regeneration and growth of sensory hair cells by locally administering generally any active ingredient able to inhibit or eliminate the action of $p21^{Cip1}$, $p27^{Kip1}$ or $p57^{Kip2}$ in the inner ear. Claims 28, 29, 31,

32, 34, 36-47, 55, 57, 58 and 62-66 encompass treatments for a broad range of diseases and conditions using a broad range of compounds, including antisense and gene therapy methods of treatment, wherein these compounds are administered directly to the ear (local administration).

The specification provides examples wherein a $p27^{Kip1}$ knockout mouse is made and cells within the corti-organ of the mouse undergo cell division and these mice have more hair cells than normal mice. This example does not provide any demonstration of a treatment for perceptive deafness, nor does it provide evidence that the inhibition of $p21^{Cip1}$, $p27^{Kip1}$ and $p57^{Kip2}$ results in promoting regeneration or proliferation of sensory hair cells. There are no examples wherein any inhibitor of a cell cycle inhibitor, including $p21^{Cip1}$, $p27^{Kip1}$ or $p57^{Kip2}$ is administered to a subject. There are no examples wherein $p21^{Cip1}$ or $p57^{Kip2}$ activity is knocked out or even reduced and sensory cell growth is affected. There are no examples wherein perceptive deafness is treated by inhibition of a cell cycle inhibitor. There are no examples wherein antisense a gene therapy vector is delivered in vivo to an ear, even by local administration, nor wherein antisense or gene therapy methods are used to provide a treatment effect for any disease or disorder of the inner ear, including perception deafness.

After the date the instant invention was made, the inventor of the instant application states, "A causal therapeutic option for sensorineural hearing loss is not yet available....A specific therapeutic modality directly applicable to the inner ear has yet to be developed." and "At present the only available therapeutic option is symptomatic in the form of hearing aids." (Pfister and Löwenheim, 2002, p53, center column).

The morphological development of the inner ear involves a complex series or developmental events (See for example, Chen et al.) and at the time the instant invention was made "the mechanisms that link developmental events to the cell cycle machinery that controls cell proliferation remain poorly understood" (Chen et al., p 1581, introduction, first column). Although cyclin-dependent kinase inhibitors were known to be involved in developmental events in the inner ear, "In spite of the advances in our knowledge of the regulation of CDK activity, little is known about how regulation of CKIs is integrated into specific developmental programs to coordinate cell proliferation with morphogenesis." (Chen et al. p 1582, first column). To provide a treatment effect for a disease or disorder of the inner ear, as claimed, it would require not only hair cell proliferation, but additionally differentiation, maturation, functional recovery and maintenance of the sensory cells. Although the specification demonstrates a role for one particular cell cycle kinase inhibitor in sensory cell development, the signaling pathways had not been elucidated to achieve control of the development of these cells in a specific manner and it was unclear whether the release of cells from inhibition of proliferation would initiate the further events required to complete the hair cell regeneration process (see for example, Löwenheim et al., PNAS, 96, 1999, page 4088, last paragraph), as would be required to achieve a treatment effect for a disease or disorder of the inner ear. The specification has not provided any guidance by which one skilled in the art would know how to administer inhibitors for cell cycle inhibitors to control this process, in order to provide a treatment effect, including a treatment for perception deafness, as claimed, or in a process of promoting regeneration and growth

of sensory hair cells, as claimed. Further, the preferred target for inhibition in the specification, $p27^{Kip1}$, appears to have roles not only in development, but also in cell maintenance (see for example, Chen et al.). The specification has not provided any information on how to specifically inhibit $p27^{Kip1}$ for regeneration, without affecting its role in cell maintenance, such that the outcome of administration of an inhibitor would be a treatment for perception deafness. Further, the specification has provided no guidance with respect to how the other specifically claimed cyclin dependent kinase inhibitors ($p21^{Cip1}$ or $p57^{Kip2}$) are involved in the growth and maintenance of sensory hair cells. Given the complexity of the pathways of sensory cell development, and the lack of available information on the timing and role of cell cycle inhibitors in these pathways, the skilled artisan would not be able to predictably control the development of these cells by administering inhibitors of $p21^{Cip1}$, $p27^{Kip1}$ or $p57^{Kip2}$, such that a treatment effect for perception deafness would be achieved, or such that hair cell growth would be promoted in a manner to result in sensory hair cells effective in the treatment methods claimed, without undue trial and error experimentation.

In order to practice the invention as claimed, the skilled artisan would need to under undue trial and error experimentation to determine how to control sensory cell development by administering inhibitors of cell cycle inhibitors, for example, which of the specifically claimed cyclin dependent kinase inhibitors to target for particular diseases and disorders resulting in perceptive deafness, how to specifically target a particular cell cycle inhibitor, how long to administer a particular inhibitor, and when to turn off and on particular cell cycle inhibitors to achieve a particular morphology, for example, in order

to provide a treatment effect or to regenerate or provide growth of active sensory hair cells. Therefore, due to the breadth of the claims, the nature of the invention, the unpredictability recognized in the art, the lack of specific guidance and working examples in the specification and the quantity of experimentation required for the skilled artisan to practice the claimed invention, one skilled in the art would not be enabled to practice the claimed methods of treatment and regeneration.

In response to the rejection of claims 28, 29, 31-48, 55-58 and 62 under 35 USC 112, first paragraph, set forth in the prior Office action, Applicant argues that the claims are enabled by the specification on the treatment of perceptive deafness by inhibiting $p21^{Cip1}$, $p27^{Kip1}$ or $p57^{Kip2}$ by locally administered inhibitors. These arguments have been considered as they apply to the rejection of claims 28, 29, 31, 32, 34, 36-47, 55, 57, 58 and 62-66 under 35 USC 112, first paragraph, set forth herein, but have not been found to be persuasive.

Applicant argues that the specification provide specific guidance on the treatment of perception deafness, defined as the complete or partial loss of hearing due to the damage or destruction of sensory hair cells, which can be treated by the regeneration of sensory hair cells. This argument is not found persuasive because, as defined, perceptive deafness encompasses a broad range of diseases and disorders, including for example, deafness caused by destruction of sensory cells wherein the origin of the destruction is genetic, unrelated to cell cyclin inhibitors.

Applicant argues that the specification describes how inhibitors of cyclin-dependent kinase inhibitors $p21^{Cip1}$, $p27^{Kip1}$ or $p57^{Kip2}$ can be used to stimulate or initiate that regeneration. The guidance in the specification, however, is not specific and does not address other aspects of hair sensory cell regeneration, for example, maturation and development of these cells. As discussed in the rejection of record, initiation of proliferation or stimulation of proliferation is not sufficient to result in sensory hair cells that are effective to treat hearing loss. Applicant's arguments do not address this aspect of the rejection.

Applicant argues that the specification provides experimental evidence that the genetic deletion of $p27^{Kip1}$ results in the on-going proliferation of sensory hair cells and that hair cell proliferation can be stimulated by otoxic injury in mice with a heterozygous deletion of $p27^{Kip1}$. Applicant argues these examples are evidence that inhibition $p27^{Kip1}$will result in support hair cell proliferation and regeneration. These arguments are not persuasive because the experimental evidence does not address the scope of the claimed methods. The claims are directed to methods wherein $p21^{Cip1}$ or $p57^{Kip2}$ are inhibited, but these experiments are only directed to $p27^{Kip1}$. There is no evidence to suggest that the results seen for $p27^{Kip1}$ correlate broadly for the other specifically claimed enzymes. Further, the proliferation observed in the mouse models used in the specification are the result of an absence of $p27^{Kip1}$ from birth, throughout development. It is unclear that the same proliferation effects would occur in sensory hair cells when trying to reverse a dormant state of the cells, which matured and developed in the presence of $p27^{Kip1}$, for example, whether proliferated cells would have the same

potential to mature or the same morphology. Finally, the experiments in the specification only demonstrate proliferation and do not discuss if the resultant cells are properly developed, providing viable sensory cells that result in a treatment for perceptive deafness, as claimed.

Applicant argues that the specification provides guidance with respect to the specific inhibitors $p21^{Cip1}$, $p27^{Kip1}$ or $p57^{Kip2}$, as claimed, including specific peptides that interfere with interactions between $p27^{Kip1}$ and CDK2 or cyclin A, including a specific 15 amino acid peptide and points to pages 5 and 6 for that specific guidance. Applicant argues that with respect to $p21^{Kip}$ or $p57^{Kip2}$ the prior art teaches that members of the KIP/CIP family have a 65 amino acid region of homology (38%-44%) at the N-terminal region which is necessary and sufficient to bind to and inhibit cyclin-dependent kinases. Applicant argues that the specification is not required to disclose every species encompassed in the invention. These arguments have not been found to be persuasive because the specification does not provide specific inhibitory peptides, even at page 5 and 6, the citations directed to peptides do not teach specific inhibitors, but rather provides a prophetic suggestion to make peptide inhibitors with a particular activity. There are no actual inhibitors disclosed in the specification with the activity suggested. Further, the arguments directed to the homology among KIP/CIP family members do not seem relevant to the rejection of record. Despite some degree of homology in a short portion of these peptides, they have different roles in the development and maturation of hair cells and it require specific guidance for the inhibition each of these individual cell cyclin kinase inhibitors for use in treating perceptive deafness, as claimed.

Applicant argues that the amendments limiting the claims to local delivery overcome the reference Jen et al. as cited to support that systemic delivery of antisense is unpredictable and argues that Branch teaches that the non-antisense effects of oligonucleotides can stimulate the immune system. The aspects of the rejection directed to systemic delivery of antisense and vectors has been withdrawn, as local delivery to the ear, as claimed, was enabled in the art at the time of filing. It is unclear how immune stimulation is related to the instantly claimed methods, which are directed to sensory hair cell regeneration, and this argument seems off-point.

Although the amended claims are directed specifically to $p21^{Cip1}$, $p27^{Kip1}$ or $p57^{Kip2}$ and further to locally administered inhibitors, it is clear from the art that hair cell development is very complex and would require modulation of multiple hair cell growth and development factors, at the proper time, to result in the regrowth of viable sensory hair cells in a pattern effective to result in a viable structure to treat perception deafness. Applicant's arguments do not appear to address this aspect of the rejection of record.

Applicant argues that the declaration by Dr. Jonathan Kill, filed March 11, 2003 provides specific guidance with respect to specific antisense for use in the claimed methods as well as appropriate concentrations for a therapeutic result and that the specification describes that DNA and RNA can be delivered in vivo with the aid of liposomes and gives an approximate concentration for use. Applicant notes that the use of antisense molecule SPI5101 was known in the art at the time of filing. Applicant argues that the declaration filed March 11, 2003 and the specification which provides

details on delivery to the perilymphatic space on page 7, enable local delivery. Although local delivery to the perilymphatic space was enabled in the art, delivery is not the only aspect of the rejection of record. The guidance in the specification does not provide enablement for the development and maturation of sensory hair cells, as required for the treatment of perceptive deafness claimed. The declaration filed March 11, 2003, does not address this aspect of the rejection of record.

The Declaration under 37 CFR 1.132 filed March 11, 2003 is insufficient to overcome the rejection of 28, 29, 31, 32, 34, 36-47, 55, 57, 58 and 62-66 under 35 USC 112, based upon 35 USC 112, first paragraph, as lacking enablement, as set forth herein because: The Declaration does not address the scope of the claims. The experiments provided in the Declaration demonstrate inhibition of one cell cycle inhibitor $p27^{Kip1}$ using antisense delivered locally to the ear and the result is proliferation of cells in the organ of Corti in two out of five test animals. This does not address the scope of the claims, which are directed to methods of treatment for perceptive deafness and include gene therapy vectors, and methods wherein $p21^{Cip1}$ or $p57^{Kip2}$ are inhibited. The Declaration does not provide any guidance for treatment methods nor does it demonstrate a treatment for perceptive deafness. The experiments in the declaration only demonstrate stimulation of proliferation of sensory hair cells. As discussed in the rejection of record, to result in a treatment for perceptive deafness, the sensory hair cells require proper development and maturation of the cells, which is a complex and unpredictable process. It is unclear that the cells have done anything more than proliferate, which would not be effective for a treatment method, as claimed.

Additionally, the methods provided in the declaration use methods which were not described in the specification as filed. For example, the specification does not describe the specific antisense used, nor is that antisense provided in the concentration range specified by the specification. Although Applicant argues that SPI5101 was known in the art, the prior art does not describe using this antisense as described in the declaration. Further, the declaration discusses SPI 5505 as the superior antisense, optimized for use in the methods. SPI5505 was not described in the specification.

Claims 28, 29, 31, 32, 34, 36-47, 55, 57, 58 and 62 are maintained as rejected and claims 63-66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 28, 29, 31, 32, 34, 36-47, 55, 57, 58 and 62-66 are drawn to active ingredients that inhibit cyclin-dependent kinase inhibitors $p21^{Cip1}$, $p27^{Kip1}$ or $p57^{Kip2}$ in the inner ear, and methods that require these active ingredients. These active ingredients claimed, and methods claimed that require these active ingredients, encompass a very broad genus of compounds with highly variant structures. For example, the genus of active ingredients would encompass many types of inhibitors, including proteins, peptides, nucleic acids encoding proteins, inhibitory nucleic acids, small molecule inhibitors, and antibodies, and would encompass direct or indirect

inhibitors of these specific cell cycle inhibitors, each of which would have a different structure.

The specification has not provided the structure of any active ingredient encompassed by the claims. For example, although the specification suggests the preferred embodiment of the claimed active ingredients would be inhibitors of $p27^{kip1}$, the specification has not provided any structure for inhibitors of $p27^{kip1}$, for example, there is no sequence for an antisense inhibitor, no mRNA sequence by which an antisense sequence could be determined, no amino acid sequence or structural information for a peptide inhibitor of $p27^{kip1}$, and not structural information has been provided for a small molecule inhibitor of $p27^{kip1}$. Similarly, the specification does not provide the detailed chemical structure of inhibitors of the other specifically claimed cell cycle inhibitors, $p21^{Cip1}$ or $p57^{Kip2}$. The genus of active ingredients claimed is so broad that it may encompass compounds known in the prior art, however, the specification has not provided sufficient description such that the skill artisan would recognize which prior art compounds have the desired activity, nor does the prior art provide a written description for the very broad genus claimed.

The specification has not provided the detailed chemical structure or common structural characteristics of these active ingredients, such that the skilled artisan would recognize that the inventor was in possession of the broad genus of active ingredients claimed, or required to practice the claimed methods, at the time the instant invention was made.

In response to the rejection of record under 35 USC 112, first paragraph, lack of adequate written description, set forth in the prior Office action, Applicant argues that Applicant argues that the written description requirement may be met by disclosure of functional characteristics when coupled with a known or disclosed correlation between structure and function according to Enzo Biochem. V. Gen-Probe Inc. Applicant argues that structure of the pending claimed compounds does correlate with function and discusses the similarity of structure and function of KIP/CIP family members and the specifically claimed cell cycle kinas inhibitors $p21^{Cip1}$, $p27^{Kip1}$ and $p57^{Kip2}$. Applicant cites prior art references that disclose the structure of these proteins. The attachments to the response cited by Applicant were not provided, however, these arguments do not address the written description rejection of record. The claimed methods require the use of compounds that inhibit the cell cycle inhibitors $p21^{Cip1}$, $p27^{Kip1}$ or $p57^{Kip2}$. These compounds were not described in the specification or in the prior art. The structure of $p21^{Cip1}$, $p27^{Kip1}$ and $p57^{Kip2}$ does not provide description for the broad genus of compounds that inhibit these cell cycle inhibitors.

Applicant further argues that inhibitors of the KIP/CIP family were known in the art at the time of filing and cites references that disclose inhibitors. These references, however, were not provided with the response filed. Applicant cites Coates et al. and Hauser et al., already of record in the case, as disclosing antisense, protein and antibody inhibitors of $p27^{Kip1}$ and therefore the skilled artisan would recognize possession of the claimed invention and US Patent No 5,688,665. These references disclose only a very small number of species within the genus, and each of the

disclosed species in these references is an inhibitor of $p27^{Kip1}$ and do not describe the genus of compounds encompassed in the compositions claimed and used in the methods of treatment claimed. Inhibitors of $p21^{Cip1}$ and $p57^{Kip2}$ are not described, and the genus of $p27^{Kip1}$ inhibitors is not described, for example, peptide inhibitors and highly variant small molecule inhibitors are not described by structure.

Applicant further argues the specification describes various inhibitors, however, the specification only describes these inhibitors generally, by class of compounds, and does not provide any detailed chemical structure or common characteristics of these compounds, such that the skilled artisan would recognize that the inventor was in possession of the broad genus of compounds claimed and used in the claimed methods of treatment.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 55 is maintained as rejected under 35 U.S.C. 102(b) as being anticipated by Hauser et al. (Cell Growth and Differentiation, Vol. 8, Feb 1997, p 203-211).

Hauser et al. disclose nucleic acids inhibitors of cell cycle inhibitors, including antisense targeted to $p27^{kip1}$ in a solution comprising a pharmaceutically acceptable carrier (for example, a solution comprising water, KBM media, see for example page 210, second column). Hauser et al. do not disclose that these inhibitors have sensory

cell regeneration properties, however, these inhibitors have all of the characteristics of the claimed active ingredients and are active against $p27^{kip1}$, the preferred embodiment of the instant specification and, therefore, would inherently have the activity claimed. The specification is silent with regard to the concentration of antisense required to be therapeutically effective, however, the concentration of antisense in the composition disclosed by Hauser et al. is effective for inhibition of $p27^{kip1}$, which is the effect set forth in the specification for a therapeutic effect and is at a concentration higher than the concentration used in Applicant's declaration submitted March 11, 2003, and therefore, would be considered to be in a therapeutically effective amount. Therefore, Hauser et al. anticipates claim 55.

In response to the rejection under 35 USC 102(b) as anticipated by Hauser et al. set forth in the prior Office action, Applicant argues that Hauser et al. is not an enabling reference because Hauser et al. does not disclose the composition of KBM media, nor does the supplier of KBM media (Clonetics) disclose the ingredients of KBM (supported by Attachment G, which was not provided). Applicant further argues that the KBM media disclosed by Hauser et al. is not intended or approved for human or veterinary use, as supported by Attachment F, which was not provided.

This is not found to be persuasive because the composition of KBM is not required to enable the composition of Hauser et al. KBM media is commercially available, as noted by Applicant, and the skilled artisan could easily make the composition disclosed by Hauser based on their disclosure. Attachments F and G,

relied upon to support Applicant's arguments have not been provided. Although Applicant argues a disclaimer statement that KBM is not approved or intended for use in humans or animals supports that KBM is not pharmaceutically acceptable, the disclaimer does not mean that the composition disclosed by Hauser et al. does not have pharmaceutical properties, for example, when delivered locally. The composition disclosed by Hauser et al. comprises a pharmaceutically acceptable carrier (e.g. water) and a concentration of $p27^{kip1}$ antisense consistent with the concentration the specification indicates is therapeutically acceptable and, therefore, would be expected to have the properties of the claimed composition. Applicant has not provided evidence to suggest otherwise.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (571) 272-0759. The examiner can normally be reached on Monday-Thursday 7:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at (571) 272-0760. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
February 9, 2004

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER